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Original research article

Evaluation of high-grade astrocytoma recurrence patterns after radiotherapy in the era of temozolomide: A single institution experience

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ABSTRACT

Aim: Evaluating the recurrence patterns of high-grade astrocytomas in patients who were treated with radiotherapy (RT) plus temozolomide (TMZ).

Background: The current literature suggests that reducing the margins added to the CTV does not significantly change the risk of recurrence and overall survival; thus, we decided to analyze our data and to examine the possibility of changing the adopted margins.

Materials and methods: From February 2008 till September 2013, 55 patients were treated for high-grade astrocytomas, 20 patients who had been confirmed to have recurrence were selected for the present study. Post-operative MRI was superimposed on the planning CT images in order to correlate the anatomical structures with the treatment targets. Recurrences were defined according to the Response Assessment Criteria for Glioblastoma. The mean margins of the $PTV_{initial}$ and PTV_{boost} were 1.2 cm and 1.4 cm, respectively. The analysis of the percentage of the recurrence volume (Vol_{rec}) within the 100% isodose surface was based on the following criteria: (I) Central: >95% of the Vol_{rec}; (II) In-field: 81–95% of the Vol_{rec}; (III) Marginal: 20–80% of the Vol_{rec}; and (IV) Outside: <20% of the Vol_{rec}.

Results: Of the 20 patients, 13 presented with central recurrences, 3 with in-field recurrences, 2 with marginal recurrences and 2 with outside recurrences. Therefore, the lower Vol_{rec} within 100% of the prescribed dose was considered in the classification.

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Conclusions: Of the selected patients, 80% had ≥81–95% of the Vol_{rec} within 100% of the prescribed dose and predominantly had central or in-field recurrences. These results are comparable with those from the literature.

1. Background

According to the classification of the World Health Organization, anaplastic astrocytoma (AA) and glioblastoma (GBM) correspond to high-grade astrocytomas (grades III and IV, respectively) and are associated with a mean survival of approximately 14 months.[1] Treatment with surgery is indicated in most cases and the surgical resection should be as complete as possible. Adjuvant fractionated radiotherapy (RT) is considered a standard treatment for high-grade astrocytomas, which is supported by level 1 evidence. In most cases, the therapy is divided into 30 fractions that are distributed over 6 weeks, with a total dose of 60 Gy.[1–3]

International Commission on Radiation Units and Measurements[4] recommend for the initial RT for high-grade astrocytoma, two clinical target volumes (CTVs) delineated by magnetic resonance imaging (MRI). In the first phase of treatment, an initial CTV ($CTV_{initial}$) is defined that accounts for edema and potential areas of microscopic infiltration in a T2-weighted fluid attenuated inversion recovery (FLAIR) image. In the second phase of treatment, a boost CTV (CTV_{boost}) is defined based on the surgical cavity of the T1-weighted post-operative MRI, after the administration of an intravenous contrast medium. To account for possible intrinsic geometrical errors in the system, a margin is added in all directions, which corresponds to the initial and boost planning target volumes (PTVs).

The best therapeutic results have been obtained when the chemotherapeutic agent temozolomide (TMZ) was administered concomitant/adjuvant to RT.[5] The exposure of TMZ reduces the DNA-repair enzyme 0[6] methylguanine-DNA methyltransferase (MGMT) stepping forward in the long term survival rate of patients.[6] A randomized phase III EORTC protocol compared the use of concomitant TMZ to RT alone.[7] Concomitant TMZ resulted in an increase in the mean survival from 12.1 to 14.6 months with minimal additional toxicity, and 20% of the patients had a survival rate of up to 36 months. Furthermore, TMZ has been used in recurrent cases due to its being well tolerated and having good oral bioavailability.[8]

Therapeutic success hinges on a balance between the risks and benefits inherent to treatment. In RT, delineation of the tumor or tumor cavity, and margins that are added to the delineation, are required because of the possible toxicity to healthy tissues adjacent to the lesion. These additional margins should account for the possibility of subclinical disease as well as intrinsic errors in the system, in order to reduce the probability of tumor recurrence.[3,8] The current literature suggests that reducing the margins added to the CTV does not significantly change the risk of recurrence and overall survival.[9]

2. Aim

In this study, we aimed to retrospectively evaluate the recurrence patterns of high-grade astrocytomas in patients who underwent RT and TMZ when the recurrence was within, near, or outside the adopted margins, and to examine the possibility of either reducing or increasing the adopted margins.

3. Materials and methods

3.1. Patients

From February 2008 till September 2013, 55 patients were treated for high-grade astrocytomas at a RT clinic in Florianópolis-SC Brazil. 20 patients who had been confirmed to have recurrence were selected for the present study. All those patients were more than 18 years of age, underwent RT and concomitant/adjuvant TMZ and presented a follow-up of at least 12 months. Patients who had previous treatments in other centers or who did not present recurrence confirmed by MRI were not selected. This study was approved of the Research Ethics Committee – CEPON – SC (CAAE: 32293814.9.0000.5355).

3.2. Chemo and radiotherapy procedures

The treatment protocol consisted of RT (starting 2–4 weeks after surgical resection of the tumors) plus continuous daily chemotherapy with TMZ (75 mg/m^2 of body-surface area/day, 7 days per week from first to the last day of RT) followed by adjuvant TMZ for 6 cycles (150–200 mg/m^2/5 days during each 28-day cycle). All patients underwent computed tomography (CT) simulation with a section thickness of 0.625 cm, in the supine position on a scanning table. For delineation, post-operative MRI images were superimposed on the planning CT images in order to correlate the anatomical structures with the treatment target sites.

Delineation of the tumor cavity in each case was performed manually, section by section, by an experienced radiation oncologist, and the T1-weighting after the administration of an intravenous contrast medium was considered. For this volume, a margin corresponding to the PTV_{boost}, or a PTV of 60 Gy was adopted that received the total prescribed dose. We used the margins of post-surgical edema was analyzed in a T2-weighted FLAIR image and the margin accounted for the edema corresponding to the $PTV_{initial}$, or a PTV of 46 Gy. In some cases, when the pre-operative MRI results were accessible, a correlation between the tumor resection cavity and the tumor was performed in order to cover areas with possible subclinical disease.